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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,255	01/18/2007	Yoshio Umezawa	2006_1324A	6659

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EXAMINER	
GAMETT, DANIEL C	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
12/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,255	UMEZAWA ET AL.	
	Examiner	Art Unit	
	DANIEL C. GAMETT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *9,12 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 10, and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 January 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner of your application in the USPTO has changed within Art Unit 1647. The Examiner for this Application is now Daniel C. Gamett, Ph.D..

2. Applicant's election of Group I, claim(s) 1-6, 7 in part, 8, 10 in part, 11 drawn to a probe for detecting an agonist or an antagonist to a nuclear receptor and an *in vitro* method for screening for an agonist or an antagonist, in the reply filed on 05/08/2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Applicant's election of species, "peroxisome proliferator-activated receptor" in the reply filed on 09/17/2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Upon further consideration, the requirement for election of species is hereby withdrawn.

4. Claims 9, 12, and 13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the replies filed on 05/08/2009 and 09/17/2009.

5. Claims 1-8, 10, and 11 are under examination insofar as they read upon a probe for detecting an agonist or an antagonist to a nuclear receptor and an *in vitro* method for screening for an agonist or an antagonist.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-8, 10, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weatherman et al., Mol. Endocrinol. 2002 Mar; 16(3):487-496, taken together with Sato et al., Nat. Biotechnol. 2002 Mar; 20(3):287-294 and Honda et al., Proc Natl Acad Sci U S A. 2001 February 27; 98(5): 2437–2442.

8. The instant claims are drawn to a probe for detecting an agonist or an antagonist to a nuclear receptor, which comprises a ligand-binding domain of the nuclear receptor connected with a binding-responsive site containing a peptide chain that specifically binds to a coactivator-binding site in the ligand-binding domain by a flexible linker to construct a fusion structure [ligand-recognition site/linker/binding-responsive site], and two reporters are connected with the respective ends of the fusion structure. Dependent claims 4 and 5 recite embodiments wherein the binding-responsive site is a nuclear receptor interaction domain peptide of steroid receptor coactivator 1, or specifically contains the motif of SEQ ID No: 1 (LXXLL). Dependent claim 6 recites that two reporters are a yellow fluorescent protein and a cyan fluorescent protein.

9. Citing earlier studies, Weatherman et al. teach that many coactivators that interact with the E2-activated estrogen receptor (ER) contain one or more copies of the consensus sequence,

LXXLL, and that structural studies have shown that an isolated LXXLL peptide will interact with a hydrophobic cleft that forms on one surface of the E2-bound ER. This hydrophobic cleft constitutes the activation function AF-2, which is conserved amongst nuclear receptors (paragraph bridging p.487-488). Weatherman et al. studied the interaction of ERα, fused to the red fluorescent protein (RFP) with LXXLL peptides, fused to the cyan (CFP) or green (GFP) fluorescent proteins. The basis for using these fusion proteins is that X-ray crystallographic structures of LXXLL bound to ER predict that, if LXXLL binds directly to ER, the CFP fluorophore should project toward RFP fused to the carboxy terminus of ERα. This positioning would be optimal for FRET from the CFP donor to the RFP acceptor (paragraph bridging columns on p.488). Using these reagents, ER activation was observed in the cellular environment by measuring the FRET intensity, which was promoted by E2 but or blocked by tamoxifen and another selective ER modulators (Figures 4 and 5; Table 1).

10. The reagents and methods disclosed by Weatherman et al. differ from the instantly claimed products and methods in that Weatherman et al. supply the fluorescent reporters on two interacting fusion proteins, whereas the instant claims recite that the interacting components are tethered together by a linker to form a single fusion construct.

11. Sato et al. developed genetically encoded fluorescent indicators, named "phocuses". Two different color mutants of green fluorescent protein (GFP) were joined by a tandem fusion domain composed of a substrate domain for the protein kinase of interest, a flexible linker sequence, and a phosphorylation recognition domain that binds with the phosphorylated substrate domain. Intramolecular interaction of the substrate domain and the adjacent phosphorylation recognition domain within a phocus was dependent upon phosphorylation of the substrate

domain by protein kinase, which influenced the efficiency of fluorescence resonance energy transfer (FRET) between the GFPs within a phocus (see Abstract). Thus, a "phocus" disclosed by Sato et al. operates on the same generic principle as the instantly claimed probe. In each case, a signaling event of interest (phosphorylation in a phocus, ligand binding in the instant case) causes a conformational change that stabilizes the interaction between binding partners built into a single polypeptide, which brings fluorescent reporters located at each end of the polypeptide into proximity, which is detected by FRET. Given that all of the required binding and conformational changes are known to occur when separate ER and LXXLL fusion proteins interact (Weatherman et al.), one of skill in the art would expect to successfully substitute these interacting domains for the substrate and phosphorylation recognition domains of the Sato et al. constructs, thereby arriving at instantly claimed probes and methods. Furthermore, the skilled artisan would be motivated to do so in order to achieve the same advantages described by Sato et al. Sato et al. teach that using a single polypeptide chain with genetically encoded fluorophores is advantageous not only for imaging signaling in single live cells with high spatial and temporal resolution, but also for multicell analysis aimed at high-throughput screening.

12. Thus, Weatherman et al. and Sato et al. together provide teaching, suggestion, and motivation, and expectation of success to arrive at the instantly claimed probes and methods. The Honda et al. reference is cited as further showing that the general strategy of sandwiching a conformationally sensitive domain between two mutants of green fluorescent protein to modulate fluorescence resonance energy transfer between the latter, has been applied to creating genetically encoded indicators of signaling through cGMP-dependent protein kinase, and other intracellular second messengers (see Abstract, and p.2437, right column, 1st full paragraph). This

further supports the expectation of substituting the ER and LXXLL interacting domains described in Weatherman et al. for the substrate and phosphorylation recognition domains of the Sato et al. constructs. Therefore, the instantly claimed probes and methods are prima facie obvious in view of the combined teachings of the cited prior art.

Conclusion

13. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD., whose telephone number is (571)272-1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel C Gamett/
Examiner, Art Unit 1647